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A comparative *in vitro* evaluation of enteropolymers for pulsatile drug delivery system

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Abstract

Enteric coatings are pH sensitive and can be considered as a pulsatile drug delivery system because of the lag time is essential for the drugs that undergo degradation in gastric acidic medium which irritate the gastric mucosa. The present study explores the comparative utility of the enteropolymers (enteric-coated polymers) such as acrycoat L-100, acrycoat S-100, ethyl cellulose (EC) and cellulose acetate phthalate (CAP) in developing a suitable dosage form, exhibiting a minimum drug release in the upper regions of the gastrointestinal tract (GIT) on order to provide site specificity as well as time controlled formulation. Core tablets of diclofenac sodium (DS) were prepared by wet granulation and coated with one of the coating polymers to a varying coating level. From the dissolution data obtained, it was found that the dissolution rate was inversely proportional and lag time was directly proportional to the coating level applied. Comparative dissolution data revealed that, of all the various polymers at varying coating level used, a 15% acrycoat S 100 and EC was most suitable for pulsatile drug delivery. Moreover, such study also provides a site specific drug delivery.

Key words: Pulsatile drug delivery, enteropolymers, site specific, lag time, *in vitro* drug release.

Introduction

Enteric coatings are pH sensitive and have traditionally been used to prevent the release of a drug in the stomach. Enteropolymers (enteric-coated polymers) protect a dosage form from the acidic environment of the stomach and allow drug delivery to the small or large intestine (site specific drug delivery), depending on their dissolution pH and the thickness of the coating applied. Although enteric-coated formulations are used mainly in connection with site-specific delivery, as utilized in time-controlled drug administration, when a lag time is needed (Robinson and Lee 1987).

Enteric coating can be considered as a pulsatile drug delivery system because the lag time is essential for the drugs that undergo degradation in gastric acidic medium, cause gastric irritation, some drugs which induce nausea or vomiting, all such drug requires drug release after lag time. Pulsed fashion can be achieved by the enteric coating of delivery system. It can also be used for chronotherapeutic time controlled systems when a lag-time is needed for drug release (Wilding et al. 1994).

In recent years considerable attention has been focused on the development of pulsatile drug delivery system via enteric coating.

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Such system offers many advantages over conventional oral drug delivery systems like patient compliance, reduced dosage, and reduced dosage frequency, avoidance of side effects, avoidance of peak and valley fluctuation, nearly constant drug level at the target site. The lag time of the pulsatile release tablets could be controlled by the coating level of polymer applied which is turn related to the permeation and mechanical properties of the polymer coating (Gazzaniga et al. 1995).

Chronotropic® system is one of pulsatile drug delivery system consists of a core containing drug reservoir coated by a hydrophilic polymer hydroxylpropylmethylcellulose (HPMC) (Giordano et al. 1994). An additional enteric-coated film is given outside this layer to overcome intra-subject variability in gastric emptying rates. The lag time and the onset of action are controlled by the thickness and the viscosity grade of HPMC (Sangalli et al. 1999). In the treatment of nocturnal asthma a Salbutamol formulation containing a barrier coating which is dissolved in intestinal pH level above about 6, has successfully been used (Bogin and Ballard 1992). Furthermore Sinha et al. designed a pulsatile system by using fast release enteric-coated tablets for targeted drug delivery of celecoxib for prophylaxis of colorectal cancer.

Objectives

The present study explores the comparative utility of the enteropolymers such as acrycoat L-100, acrycoat S-100, ethyl cellulose (EC) and cellulose acetate phthalate (CAP) in developing a suitable dosage form, exhibiting a minimum drug release in the upper regions of the gastrointestinal tract (GIT) in order to provide site specificity as well as time controlled formulation. For such purpose, enteropolymers in varying coating level were applied and the effect of the coating level on lag time and drug release was evaluated *in vitro*. Enteropolymers such as acrycoat L-100, a methacrylic acid co-polymer type A, which is insoluble in gastric fluid and freely soluble in intestinal pH 6.0, acrycoat S-100, a methacrylic acid co-polymer type B, which is insoluble in gastric fluid and freely soluble in intestinal pH 7.0 and other polymers include CAP which is dissolved at a pH of 6.0 and EC which is a hydrophobic polymer provide an alternative polymer for such system were used in present study.

Diclofenac sodium (DS) was selected as a model drug as it is completely absorbed throughout the gastrointestinal tract after oral administration. DS is indicated for the acute and chronic treatment of signs and symptoms of osteoarthritis and rheumatoid arthritis, for the treatment of ankylosing, spondylitis, for the management of pain and primary dysmenorrhea, when prompt pain relief is desired. Historically, DS has been regarded as a potential gastric irritant, and studies have shown that the incidence of gastric intestinal side effects may increase with regular use. Enteric coating of the tablets, therefore, is desirable for preventing stomach upset or irritation in those taking daily DS therapy (Davies and Anderson 1997).

Materials and Methods

Materials

Diclofenac sodium (DS) was obtained as gift sample from Welable Parma. Ltd. Mehsana, India. Acrycoat S 100 and L 100 were obtained as gift samples from Corel Pharma Ltd. Ahmedabad, India. Ethyl cellulose, cellulose acetate phthalate, lactose, PVP K30 and Ac-di-sol were purchased from S.D. Fine Chemicals Ltd, Mumbai, India. All other chemicals used were of analytical grade.

Method

Preparation of core tablets: Core tablets of DS were prepared by wet granulation method according to compositions given in Table 1. Lactose anhydrous as the main filler, Ac-di-sol as disintegrating agent and PVP K_{30} in alcohol (IPA) was used as binder in core tablet formulation. Tablets weighing 200 mg containing 100 mg of DS were compressed using tabletting machine (rimek minipress) employing a 7.9 mm concave die-punch. Compression force was adjusted to hardness of 6-7 kg/cm^2. After ejection, the tablets were stored over silica gel in a desiccator for 24 h to allow for elastic recovery and hardening.

Table 1. Composition of core tablet

Ingredients	Quantity (%w/w)
Diclofenac sodium	50
Lactose anhydrous	39
Ac-di-sol	5
PVP K_{30}	4
Talc	1
Magnesium stearate	1
Total	**100**

Prepared core tablets were evaluated for physical properties like uniformity of weight determined by using a Sartorious electronic balance (Model CP- 224 S), hardness by using a dial type hardness tester (Model 1101, Shivani Scientific Ind), friability by using a Roche friabiliator (Camp-bell Electronics, Mumbai), disintegration time by using a disintegration test apparatus (Electrolab ED-2 Bowl USP, Mumbai), diameter and thickness by using vernier caliperse etc.

Uniformity of content

The prepared tablets were tested for their drug content. Ten tablets were finely powdered; quantities of the powder equivalent to 100 mg of DS were accurately weighed and transferred to a 100-ml of volumetric flask. Methanol was added in small quantities to the flask and mixed thoroughly. Then the volume was made up to 100 ml mark with the same solvent. The flasks were kept on a sonicator for 5 minutes. Solution was then filtered using a whatman filter paper and suitable dilution was made. The absorbance of the resulting solution was measured at the λ_{max} at 281 nm using a Systronic-2201 UV/Vis double beam spectrophotometer against blank as methanol. The linearity equation obtained from calibration curve was use for estimation of DS in the tablet formulation (Adeyene and Li 1990).

Preparation of enteric coated tablet

Preparations of coating solutions

Polymeric content in the coating solution was kept constant of 5 % w/v. For acrycoat L-100 and acrycoat S-100, polymer solutions were prepared using isopropyl alcohol (IPA) as solvent and dibutyl phthalate (DBP) as plasticizer (10% as polymer based). In the case of EC, acetone as solvent and DBP as plasticizer (10% as polymer based), while in CAP, acetone as solvent and propylene glycol (PG) as plasticizer (1.5% as polymer based) were used. Required quantity of polymer dissolved in an organic solvent and stirred on magnetic stirrer to get homogeneous coating solution. After getting homogeneous coating solution coating was done on tablets. In all polymer solution titanium dioxide (5% as polymer based) and desired color was added.

Coating of the tablets

It was done by using the standard coating pan. Fixed numbers of tablets were coated each time by atomizing the polymeric coating solution through the means of TLC spryer. The coating pan was

operated at fixed RPM for all polymeric solution. The coating solution was applied when the tablet bed in the coating pan reached ~ 60°C.

The process conditions were as follows:

Batch Size = 10 gm
Inlet temperature = 50 – 60°C
Product temperature = 35 - 40° C
Spay rate = 4 – 8 ml min^{-1}
Spray nozzle diameter = 1 mm
Distance: Tablet bed – spray gun = 10 – 15 cm
Pan speed (RPM) = 35

The coating process was repeated till the desired level of coating was achieved. The coating level was determined on the basis of % weight gain by the core tablet. The level of coating was kept constant (i.e., 8%, 15%, 24% weight gain) for all the polymers.

The % weight gain calculated by using the following equation:

$$\%\text{weight gain} = \left(\frac{W_t - W_0}{W_0}\right) \times 100 \qquad \text{---------- (1)}$$

Where W_t is the weight of the tablets after coating, W_0 is the initial weight of tablets. The tablets were dried in an oven at 50°C for 12 hr and these tablets were used for the evaluation.

Lag time of coating tablets

Coating tablets were placed into USP dissolution paddle apparatus at rotation speed 50 rpm with phosphate buffer IP pH 6.8, 37±0.5°C and observed visually. The lag time was defined as the time point, when the outer coating ruptured due to swelling.

Dissolution studies of the coated tablets

For each of the selected level of the coated tablets, six tablets were subjected to the dissolution studies. The USP NF 24 method for enteric coated tablets (basket method, 100 rpm, 37±0.5°C) using a USP dissolution test apparatus was used for each of the selected level of the coated tablets. The initial 2 h study in 900 ml of 0.1 N HCl, followed by dissolution at a pH of 6.8. Aliquots of predetermined quantity were collected manually at definite time intervals and analyzed for drug content using a UV-visible spectrophotometer at a λ_{max} of 276 nm.

Results and Discussion

Various physical parameters were evaluated. The variation in thickness, weight, hardness, friability and drug content values of all the prepared tablets in reference to average values for each parameter were found within official limits (Table 2).

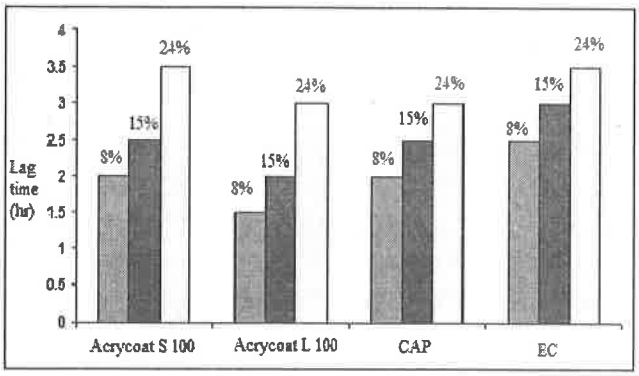
Table 2. Evaluation parameters of core tablet.

Evaluation parameter	Result
Weight variation (mg)	201± 2
Drug content (%)	99 ± 2
Hardness (kg/cm^2)	6.8 ± 0.2
Diameter (mm)	7.9 ±0.5
Thickness (mm)	4.1 ± 0.01
Friability (%)	0.82±0.2
Disintegration time (minutes)	13 ±1.0

All the values are expressed as mean ± SD.

Lag time of coating tablets

From the preliminary study it was found that all the enteric coated polymers which are being selected in present study produce less flexible and less rigid film and provides pulsatile release profile. The lag time of the pulsatile release tablets coated with all four enteropolymers was investigated and could be controlled by the coating level of polymer applied (Figure 1). The lag time depended on the coating level applied as expected because the rupture time increased with higher coating level because of the increased mechanical strength of the coating and the reduced medium permeation rate at higher coating thickness (Figure 2).



Note: error bar should be omitted for clarity

Figure 1. Effect of coating level on lag time of coated tablets.

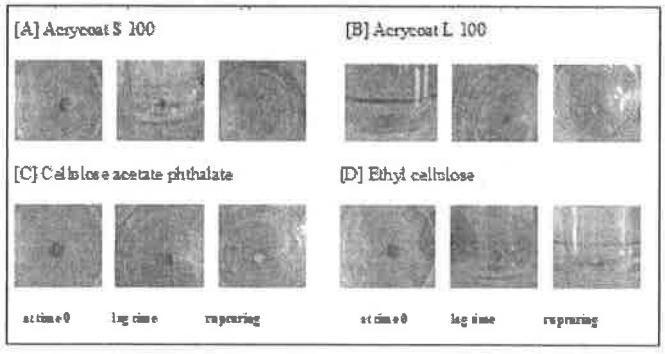


Figure 2. Rupturing behavior from pulsatile tablet coated with enteropolymers

In-vitro drug release study

All the enteropolymers showed no drug release in the first 2 h in the gastric environment. Afterwards a different drug release profile was evident for each polymer. The time at which rupture on the polymer layer in the dissolution medium was taken as an indication for the beginning of the drug release into the medium. The lag time and drug release was directly related to the concentration of polymer in solution and the coating level applied. Percent of drug release vs. time plot shows that the dissolution rate was inversely proportional to the coating level applied (Figure 3 (A), (B), (C) and (D). A significant difference was observed in the percentage of drug released for different coating level. All the coated tablets with variable coating level showed a nearly complete drug release in the 10 h-12 h.

Formulations with acrycoat S100 as enteropolymer

Percent of drug release versus time plot shows that the dissolution rate was inversely proportional to the coating level applied (Figure 3 A). At a coating level of 8%, the percent drug release in the first 3 h of dissolution at pH 6.8 (small intestinal environment and transit time) was 27.11%. Increasing the coating level to 15% and 24 % reduced the drug release to 14.21% and 2%, respectively. All the coated tablets showed a nearly complete drug release in the 12 h. Increasing the coating level of acrycoat S 100 shows a decrease in the dissolution rate of drug. This can be explained by the fact that increasing the coat concentration made the coat more impermeable and drug release was retarded. Slowly as the coating solubilized, drug dissolution through it was facilitated.

Formulations with acrycoat L100 as enteropolymer

Percent of drug release versus time plot shows that the dissolution rate was inversely proportional to the coating level applied (Figure 3 B). At a coating level of 8%, the percent drug release in the first 3 h of dissolution at pH 6.8 (small intestinal environment and transit time) was 35.03%. Increasing the coating level to 15% and 24% reduced the drug release to 18.84% and 9.5%, respectively. All the coated tablets showed a nearly complete drug release in the 10 h- 12 h.

Formulations with CAP as enteropolymer

Similarly, varying the coating level of CAP applied, the percent drug release from the tablet significantly decreases (Figure 3 C). The formulation with 8% coating level showed 25% drug release in the first 3 h of dissolution at pH 6.8. A total of 99% drug was released in the nearly 10 h. Increasing the coating level to 15% and 24 % reduce the drug release to 12.05% and 7.15%, respectively. An increase in coat concentration retarded drug release, no considerable retardation was observed. This may be attributed to the fact that the dissolution medium (pH 6.8) which is well above the pH of CAP solubilization (Sinha and Kumria 2003).

Formulations with EC as enteropolymer

Percent of drug release versus time plot shows that the dissolution rate was inversely proportional to the coating level applied (Figure 3 D). At a coating level of 8%, the percent drug release in the first 3 h of dissolution at pH 6.8 (small intestinal environment and transit time) was 8.91 %. Increasing the coating level to 15% and 24 %, there was no drug released observed. These may attributed that upon increasing the coating level, the release rate was highly suppressed, suggesting that the thicker film formed by EC was quite impermeable.

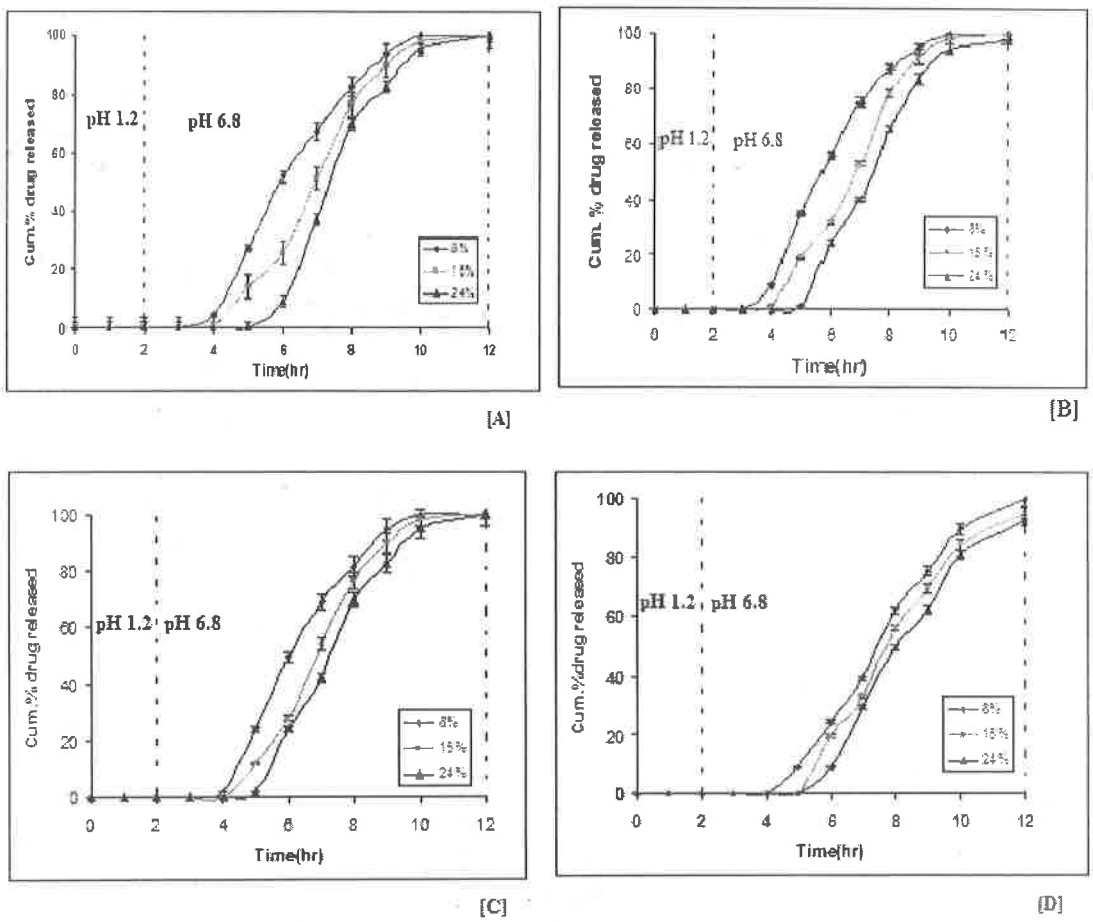


Figure 3. Cumulative percent of drug released (mean ± S.D, $n = 6$) *versus* time profile for tablets coated with: a) Acrycoat S 100 b) Acrycoat L 100 c) CAP d) EC.

Conclusion

The lag time and *in vitro* drug release profile for all the four polymer solutions at variable coating levels and constant concentration indicate that dissolution rate is inversely proportional to the coating level applied and lag time is directly proportional to the coating level applied. At the coating level of 15% acrycoat S 100 and ethyl cellulose, provided the most appropriate enteropolymers for pulsatile drug delivery in the present study. Variation in coating level can facilitate drug delivery to terminal ileum, distal or proximal colon. Moreover, such study also provides a site specific drug delivery.

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